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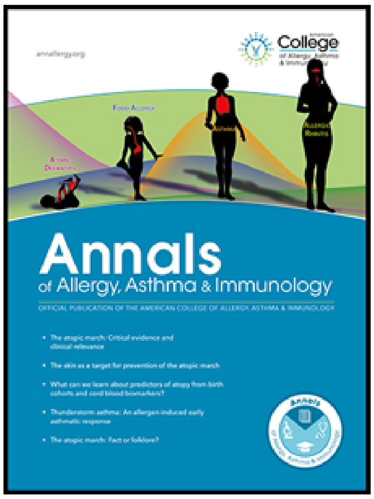

Asthma in older adults with severe COVID-19: clinical outcomes and predictors of mortality.

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Asthma in older adults with severe COVID-19: clinical outcomes and predictors of mortality.

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CCI, Charlson comorbidity index

COVID-19, Coronavirus disease

ICU, intensive care unit

SpO_2, oxygen saturation

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The study was approved by the Medical Ethical Committee of Sechenov Moscow Medical University (protocol number 08-20/5).

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To date, numerous studies have examined the relationship between COVID-19 and asthma; however, the impact of asthma on COVID-19-associated outcomes remains controversial and not fully understood[1-3]. It is possible that these contradictions can be explained in terms of asthma heterogeneity. There is data to suggest that asthma in older adults is phenotypically different from that in young patients, particularly when physiological changes associated with the aging process are taken into account[4]. Since old age is a well-known factor of a poor prognosis in COVID-19[5], it is of great interest to study the course of COVID-19 in older patients with asthma.

This observational study was conducted in the Pulmonology Department of a university-affiliated hospital between May 12, 2020, and December 27, 2020. As this was a retrospective study, the requirement for informed consent was waived. We enrolled patients over 65 years old with physician diagnosed asthma admitted with SARS-CoV-2 infection confirmed by real-time polymerase chain reaction, radiological findings compatible with severe COVID-19 pneumonia, and SpO_2 at admission <92% (on room air). The exclusion criteria were non-asthma chronic lung diseases. The diagnostic criteria of allergic asthma were those of the GINA guidelines: an exposure to the allergen induces or aggravates the symptoms, and the skin prick test and serum specific IgE test show positive responses to at least one allergen[6]. Demographic, clinical, and laboratory data was recorded at admission. We recorded the Charlson Comorbidity Index (CCI), which calculates the score for comorbidities according to the relative risks of 19 major diseases, including ischemic heart disease, diabetes, and hypertension. We also analyzed the outcomes of COVID-19, such as a transfer to the intensive care unit (ICU), need for non-invasive and invasive mechanical ventilation, and 28-day mortality.

The objectives of this study were: (1) to investigate the influence of asthma in older adults on COVID-19 outcomes, and (2) to identify predictors of in-hospital mortality of older patients

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with asthma and COVID-19. The Cox proportional hazard models were used to estimate the association between asthma and in-hospital mortality; the models were adjusted for age, sex, and comorbidities.

Of the 2,435 patients hospitalized with COVID-19 infection, 69 patients met the necessary diagnostic criteria (2.8%). Baseline characteristics of the study population are shown in Table 1. Most patients had a non-allergic asthma phenotype (44 patients, 63.8%) and multiple comorbidities (the median CCI was 5.3). Nineteen of included patients (27.5%) were receiving GINA step 4-5 therapies; 12 patients (17.4%) and 4 patients (5.8%) were treated before admission with maintenance oral steroids and biologic therapy ((omalizumab (n=2), mepolizumab (n=2)), respectively.

During hospitalization, all patients received the standard therapy including prophylactic enoxaparin, intravenous dexamethasone, and tocilizumab. Supplemental oxygen was administered in all patients (100%), non-invasive ventilation and invasive mechanical ventilation were used in 6 (8.6%) and 7(10.1%) patients, respectively. Twelve patients (17.3%) were transferred to the ICU, and the 28-day mortality rate was 13%(9 patients). All patients who died had non-allergic asthma. There was a significant difference in the proportion of patients with severe asthma among deceased and surviving patients (56% vs 13%; p=0.01). Patients who died from COVID-19 used maintenance oral steroids more often than survivors (44% vs 13%, p=0.04).

Patients who died had a significantly higher CCI, higher body temperature at admission, higher respiratory rate, and a higher baseline blood neutrophil count, neutrophil/lymphocyte ratio, fibrinogen, lactate dehydrogenase, glucose levels, and C-reactive protein at Day 5 compared to survivors. The Cox regression analysis identified the following variables predicting poor outcomes: CCI (risk ratio (RR) 1.67[1.11-2.53]), body temperature (RR 3.73[1.31-10.6]), severe asthma (RR 2.75[1.08-6.99]), non-allergic asthma (RR 7.95[1.06-

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14.30]), and the chronic oral steroid use (RR 2.57[1.01-6.53]). The risk of death was not associated with an increased or decreased eosinophil count (Cox regression; p=0.57 and p=0.53 for percentage and absolute values, respectively).

In a recently published study, Eggert and colleagues showed that among asthmatics positive for SARS-CoV-2, the allergic asthma phenotype was associated with a reduced risk of hospital admissions, meaning that certain phenotypes of asthma may be protective[7]. The role of allergic asthma diminishes with age; hence a different phenotype presents in older adults, with normal eosinophils and elevated sputum neutrophils[4]. Interestingly, in our study, all deceased patients had a non-allergic asthma phenotype. In addition, as recently shown in a study by Schleich et al., older adults with asthma are characterized by poorer lung function and higher bronchial neutrophilic inflammation[4]. Recent publications have suggested that allergic status and type 2 inflammation may decrease susceptibility to SARS-CoV-2 infection and protect against the most severe consequences of COVID-19[8]. Ferastraoaru et al. in their retrospective study demonstrated that in patients with asthma pre-existing blood eosinophilia greater than or equal to 150 cells/mL was protective from COVID-19-associated admission[9]. In our cohort of older adults with asthma, we were unable to show differences in eosinophilia levels between deceased and surviving patients. However, it cannot be ruled out that the blood eosinophil counts did not differ significantly due to the outpatient and inpatient use of systemic steroids. In our study therapy with maintenance oral steroids in older adults with asthma was a risk factor for poor prognosis. Similar data was presented in a recent study by Adir et al. who also showed that systemic steroid use was significantly associated with an increased risk of severe COVID-19 and all-cause mortality[10]. In contrast to the study by Adir et al., in our study, all patients had severe COVID-19 and all received intravenous dexamethasone during hospitalization. Despite this, a chronic use of steroids turned out to be a factor of poor prognosis.

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Our study has several limitations. It was a retrospective study performed in a single center, and statistical analysis and interpretation of our study results are further limited by its relatively small sample size.

Therefore, our study provided evidence that non-allergic asthma phenotype, asthma severity, systemic steroid use, and comorbidities may be risk factors for poor outcomes in older patients with asthma and severe COVID-19. However, further large cohort studies are needed to examine the effect of asthma severity and phenotypes on COVID-19 outcomes in older adults.

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Table 1. Demographic, clinical and laboratory characteristics of older patients with asthma and severe COVID-19.

Parameters	All patients (n=69)	Survived patients (n=60)	Deceased patients (n=9)	P value[1]
Age, years	71(67-80)	70(66-80)	72(68-85)	0.33
Gender (male/female)	30/39	24/36	6/3	0.16
Smoking history, pack-years	45(32-50)	48(45-55)	32(20-45)	0.52
BMI, kg/m^2	28.2(24.7-33.2)	28.1(23.2-33.8)	28.0(27.3-32.4)	0.69
CCI, points	5.3(4-7)	5.0(3-6)	7.0(6-7.5)	0.003
Arterial hypertension, n(%)	31(44.9%)	25(41.7%)	6(66.7%)	0.30
Ischemic heart disease, n(%)	18(26.1%)	14(23.3%)	4(44.4)	0.26
Atrial fibrillation, n(%)	25(36.2%)	20(29.0%)	5(55.6%)	0.52
Obesity, n(%)	30(43.5%)	25(41.7%)	5(55.6%)	0.42
Diabetes mellitus, n(%)	20(28.9%)	17(28.3%)	3(33.3%)	0.54

Chronic kidney disease, n(%)	9(13.0%)	6(10.0%)	3(33.3%)	0.14
Allergic asthma phenotype, n(%)	22(31.9%)	22(36.7%)	0(0%)	0.05
Oral steroids, n(%)	12(17.4%)	8(13.3%)	4(44.4%)	0.04
Biologic therapy, n(%)	4(5.8%)	4(6.7%)	0(0%)	0.58
Body temperature, ^{0}C*	37.1(36.9-37.6)	37.0(36.8-37.5)	37.8(37.5-38.5)	0.006
Respiratory rate, min^{-1}	23(22-24)	23(22-24)	25(24-26)	0.02
Heart rate, min^{-1}	83(74-94)	82(74-95)	84(75-90)	0.57
SpO_2/FiO_2	207(175-229)	209(171-229)	206(187-323)	0.64
Leukocytes, 10^9/L	6.2(4.7-8.9)	6.1(4.6-8.2)	8.9(6.1-9.3)	0.13
Neutrophils, 10^9/L	4.6 (2.8-10.8)	3.8(2.8-6.2)	7.3(5.1-8.2)	0.05
Lymphocytes, 10^9/L	0.9 (0.6-1.4)	1.0(0.7-1.4)	0.7(0.4-0.9)	0.06
Neutrophil/lymphocyte ratio	4.5(2.6-10.3)	3.5(2.3-7.2)	10.7(7.1-11.2)	0.02
Eosinophils, %	0.6(0.3-2.0)	1.0(0.3-3.0)	0.4(0.2-1.3)	0.15
Eosinophils, 10^9 /L	0.1(0.07-0.2)	0.1(0.03-0.2)	0.1(0.07-0.1)	0.46
Fibrinogen, g/L	5.1(4.2-8.9)	4.9(3.9-7.8)	11.4(10.3-12.4)	0.04
D-dimer, mg/L	0.9(0.4-1.1)	0.7(0.4-1.2)	1.0(0.8-5.0)	0.21
CRP at admission, mg/L	40.0(14.4-73.2)	34.9(10.6-70.9)	50.0(35.1-105.9)	0.17
CRP at day 5, mg/L	17.7(3.5-30.2)	8.6(2.8-24.3)	39.1(20.3-170.9)	0.007
Creatinine, µmol/L	90.8(80.2-103.3)	90.2(78.4-100.1)	97.8(82.4-110.9)	0.39
Glucosa, mmol/L	6.6(5.7-8.1)	6.5(5.5-7.8)	8.0(7.3-10.2)	0.02
ALT, U/L	28.7(17.7-42.8)	30.4(16-44)	24.5(19.2-58)	0.79
AST, U/L	34.4(25-49.6)	31.5(24.9-47.3)	36.5(28-60.5)	0.59
LDH, U/L	536(399-694)	445(382-664)	701(532-1155)	0.03
CT, % of lung involvement	30(25-70)	30(25-50)	50(25-75)	0.66

*The highest temperature during the day was recorded.
Continuous variables are presented as median value [interquartile range (IQR)].
Abbreviations. BMI, body mass index; CCI, Charlson comorbidity index; SpO_2, oxygen saturation; FiO_2, inspired oxygen fraction; C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CT, computed tomography.
[1]Mann-Whitney test was used.

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